REMARKS

Claim Amendments

Upon entry of this amendment, Claims 14, 15 and 17-21 are pending in this application. Claim 14 is currently amended herein. Claims 9, 12, 13 and 16 are cancelled herein without prejudice or disclaimer as to the subject matter disclosed therein. New claims 18-21 are added.

Support for the amended and new claims is found throughout the application as originally filed. *See e.g.*, page 8, lines 1-2; Examples and previously filed claims 16 and 17. Applicant respectfully submits the above amendments do not constitute new matter.

Withdrawn Rejections

Applicant appreciates the Examiner's indication that the enablement rejection and the anticipation rejections over von Eichborn et al. and Shachar et al. have been withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 9 and 12-17 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Office Action states that the term "JRU" is "not defined upon the first use in the presently amended claims."

Applicant has canceled claims 9, 12, 13 and 16. Applicant has also amended claim 14 to recite, "Japanese Reference Units (JRU)." In view of these amendments, Applicant respectfully requests withdrawal of this rejection.

Rejections Under 35 U.S.C. § 102

Claims 9, 12-15 and 17 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by U.S. Pat. No. 5,171,567 (hereinafter "Tara").

Applicants respectfully disagree and traverse this rejection.

Applicant has canceled claims 9, 12, 13 and 16. Applicant has also amended claim 14 to recite a "method for treating bullous pemphigoid comprising administering to a human patient in need of such treatment human interferon-γ ***intravenously*** in a daily dose of 2,000,000-4,000,000 Japanese Reference Units (JRU)." (emphasis added).

Applicants submit that Tara does not teach each and every limitation of amended claim 14. For example, Tara does not teach the administration of human interferon-γ (IFN-

γ) intravenously. Rather, Tara is specifically directed to the administration of IFN-γ "directly to the lungs ... by means of inhalation." Col. 1, lines 52-54.[1] Accordingly, because Tara does not teach each and every limitation of the claimed invention, Applicants respectfully request withdrawal of the 102(b) rejection.

Rejections Under 35 U.S.C. § 103

Claims 9 and 12-17 stand rejected under 35 U.S.C. §103(a), as being allegedly being obvious over U.S. Pat. Pub. No. 2003/0053985 (hereinafter "Shachar") in view of Tara.

Applicants respectfully disagree and traverse this rejection.

The Office Action states that "Shachar teaches that bullous pemphigoid is treated by low doses of interferon-γ," but "does not explicitly teach the claimed dosage of IFN-γ." The Office Action further states "one of skill in the art would know that if bullous pemphigoid is treated by low doses of IFN-γ, then higher do[s]es would also be effective..."

Applicants respectfully disagree.

As initial matter, Applicants acknowledge that in some cases a higher dose may enhance the effectiveness of a drug. Such effectiveness, however, hits a ceiling when the dose exceeds a particular level. It is also known in the art that a higher dose rapidly increases the risk of unwanted side-effects.

Shacher, for example, states:

> Human studies: Since high levels of IFN-γ were shown to be of potential therapeutic benefit in animal studies, such as the one described above, ***therapy employing high levels of IFN-γ has been attempted in human clinical trials for treatment of autoimmune disease. Such treatments, however, have been found to produce unacceptably severe side-effects in patients.*** Paragraph [0025]. (emphasis added).
>
> ***The undesirable side-effects of high doses of IFN-γ were also demonstrated in a human clinical trial for treatment of metastatic renal cell carcinoma***...These patients experienced major side-effects including

[1] *See also* abstract ("An improved method for treating or curing ATL...comprising ***administering*** an effective amount of interferon-γ...***via respiratory tract by inhalation***) (emphasis added); col. 1, lines 7-12 ("The present invention...relates to useful methods for the treatment of adult T cell leukemia/lymphoma...***characterized by the new route of administration i.e., inhalation.***") (emphasis added). Applicants also note that claim 16, directed to a method of administering human interferon-γ intravenously, was not rejected over Tara.

> fever and chills (75%), anorexia and fatigue (75%), nausea and vomiting (80%), leukopenia (38%) and abnormal liver function (25%). Paragraph [0028]. (emphasis added).
>
> ...in humans, as described in the Background section above, prior art treatment of the inflammatory diseases idiopathic pulmonary fibrosis and Crohn's disease was attempted with doses of 33,000 and 15,000 units of IFN-γ per kilogram body weight, respectively. ***Such high levels of IFN-γ, however, caused side-effects of such severity as to prohibit their use in humans.*** Paragraph [0194]. (emphasis added).

Shachar concludes by stating, "all prior art approaches employing IFN-γ have failed to provide adequate solutions for treating diseases associated with, and/or accompanied by, inflammation without risk of severe side-effects." Paragraph [0196].

As such, Shachar sought to remedy the limitations of the prior art. Indeed, the very problem Shachar addresses is the need to provide a method of treatment that uses "ultra low doses" of IFN-γ to reduce the risks of severe side-effects caused by high-dose IFN-γ administration. *See e.g.*, paragraphs [0001], [00030], [0038], [0188], [0196], [0197] and [0199]. Shachar discloses that "ultra low doses" of IFN-γ in the amount of 1-8,000 units per kilogram body weight or 66.7 to 533,333 IU (assuming 100 kilograms of weight) may be used for treatment.[2] *See e.g.*, paragraph [0200] and claim 1.

The claimed invention, however, is directed to administering a dose of 2,000,000-4,000,000 JRU (or 3,000,000-6,000,000 IU) — a dosage substantially higher than that of Shachar. As discussed above, Shachar is specifically directed to administering "ultra low doses" of IFN-γ and teaches away from using higher dosages. Accordingly, it would not be obvious to one of ordinary skill in the art to increase the dosage taught by Shachar to arrive at the claimed invention.

The Office Action suggests Tara would provide the requisite motivation to effectively administer a higher dosage than that taught by Shachar. *See* O.A. at 6.

Applicants respectfully disagree.

Initially, Applicants submit that one of ordinary skill in the art would not combine the teachings of Shachar and Tara. Shachar is directed to a method of treating inflammation, in general, comprising administering "ultra low doses" of IFN-γ. As discussed above,

[2] 1 IU equals 1.5 units. *See e.g.*, Applicants response filed on November 30, 3006.

Shachar sought to eliminate unwanted side-effects due to higher doses of IFN-γ. Tara is directed to entirely different method requiring a very specific administration method. Indeed, Tara is a drawn to a method for treating adult T cell leukemia/lymphoma (ALT) comprising administering IFN-γ via respiratory tract by inhalation. *See e.g.*, abstract. In view of these teachings, Applicants submit that one of ordinary skill in the art would have no reason to combine the methods of Shachar or Tara, let alone attempt to combine these references to arrive at the claimed invention — a method for treating bullous pemphigoid comprising administering to a human patient in need of such treatment human interferon-γ intravenously in a daily dose of 2,000,000-4,000,000 Japanese Reference Units.

Applicants also submit that it would be difficult for a skilled person to predict an effective dosage range for intravenous administration based on the inhalation dosage range described by Tara. It is common technical knowledge that a dosage range varies depending on the route of administration. In particular, since intravenous administration can deliver an active ingredient effectively into the blood, and that intravenous administration of a high dosage would increase a risk of side-effects, a skilled person would not have tried to apply Tara's inhalation dosage range (1,000,000-6,000,000 JRU) to intravenous administration. Accordingly, Applicants submit that one of ordinary skill in the art would have no reason to modify the teachings of Shachar to increase the dosage to the inhalation dosage range taught by Tara for any method, let alone a method of treating bullous pemphigoid_comprising intravenous administration.

The Office Action states that "although neither Shachar nor Tara explicitly teach intravenous administration, they also do not teach away from intravenous administration." O.A. at 6.

Applicants agree that Shachar and Tara do not teach intravenous administration, but respectfully disagree that they do not teach away from intravenous administration.

In the "Background" section, Tara explains that previous methods of treating ATL using intravenous administration have produced unsatisfactory results. *See* col. 1, lines 29-35. Tara thus sought to provide an improved method for administering IFN-γ for treating ATL — "characterized by the new route of administration i.e., inhalation." Col. 1, lines 7-12. Tara concludes by stating that "as compared with the conventional systemic administration

of IFN-γ, this method of treatment is a more effective method, with very slight side effects." Col. 8, lines 35-37. Accordingly, Tara teaches away from intravenous administration.

Applicants also submit that while Shachar lists bullous pemphigoid in a laundry list of conditions and diseases, Shachar fails to disclose, let alone provide any working examples of treating bullous pemphigoid by intravenous administration. In particular, Shachar only describes that colitis, an autoimmune disease of the gastrointestinal tract, may be treated by the interperitoneal administration of ultra-low doses of IFN-γ (200 units/kilogram body weight/day) in an *in vivo* study using a murine TNBS-induced colitis model. *See* paragraphs [0361]-[0364]. Accordingly, Shachar not only fails to teach intravenous administration, but teaches away from such an administration route.

Even assuming one of skill in the art had a reason to combine the teachings of Shachar and Tara, which Applicant does not concede, Applicant submits that this combination does not teach or suggest each and every claim limitation. In particular, Applicant submits that Shachar, alone or in combination with Tara, does not teach or suggest intravenous administration. Indeed, as acknowledged by the Examiner, "neither Shachar nor Tara explicitly teach intravenous administration." *See* O.A. at page 6. Accordingly, Applicants submit that the Office Action also fails to establish a *prima facie* case of obviousness because the cited references do not teach or suggest all the claim limitations. *See* M.P.E.P. §§ 2142-2143.

In view of the foregoing, Applicants respectfully request withdrawal of the obviousness rejection.

CONCLUSION

Applicants respectfully submit that claims 14, 15 and 17-21 are in condition for allowance, and such disposition is earnestly solicited. Should the Examiner believe that any issues remain after consideration of this response, the Examiner is encouraged to contact the Applicant's undersigned representative to discuss and resolve any such issues.

Respectfully submitted,

HUNTON & WILLIAMS LLP

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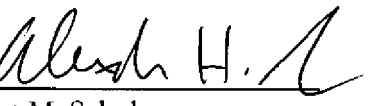
By: 

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